REMARKS

By the foregoing amendments, pages 20-21 of the specification have been amended. Also, claim 110 has been amended, and claims 114 and 115 have been added. Support for the amendments to claim 110 can be found in the specification at page 2, lines 19-22; page 3, lines 17-28; page 7, line 23 to page 9, line 34; page 11, line 17 to page 15, line 2; and page 16, lines 1-8. In particular, the intramolecular nucleophilic displacement of claim 110, step (f) is illustrated on page 13, line 14 to page 15, line 2 of the specification. Support for new claim 114 can be found at page 12, line 26 to page 13, line 5. Claims 110-114 are pending in the application.

The Informalities

The Examiner has noted several instances on pages 20-21 where clarification or correction is required. The enclosed replacement pages are believed to address all of those issues raised by the Examiner. The Examiner also mentioned that he was including annotated pages 20 and 21 with additional guidance. We have not received those annotated pages. If the enclosed replacement pages are still insufficient, Applicants request that the Examiner so advise.

The Rejection under 35 USC § 112, First Paragraph

Claim 110 stands rejected under Section 112, first paragraph, as insufficiently described and/or enabled by the specification. Specifically, the Examiner objects to the presence of "halogen" in the Markush group of Nu's. Solely in the interest of expediting prosecution, Applicants have amended claim 110 to cancel the recitation of halogen. Applicants have also deleted -O-Alk from the Markush group of claim 110.

Claim 110 is objected to because "NH_2" lacks a hyphen; this has been corrected in the claims listing. Additionally, claim 13 lacks a period; this has also been corrected.

The Rejection under 35 USC § 112, Second Paragraph

Claims 110-113 stand rejected under Section 112, second paragraph, as allegedly indefinite. Specifically, claim 110 is alleged to be indefinite because "AC" and "Ac" are

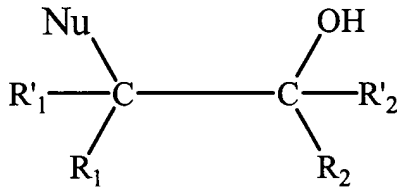
typically used to mean acetyl. In compliance with the Examiner's suggestion, claim 110 has been amended to replace "AC" and "Ac" with C_{1-7} acyl. Likewise, claim 111 has been amended to recite C_{1-4} acyl.

The Rejection under 35 USC § 102(b)

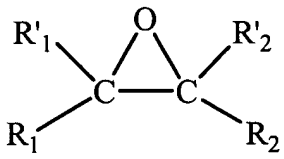
Claims 110-113 stand rejected under Section 102(b) as anticipated over Webb et al., U.S. 4,659,774.

Webb et al., U.S. 4,659,774, describe a polymer-linker for use in oligonucleotide synthesis. In one embodiment, the polymer has oxirane moieties, which are attacked by a linker group with amines at either end. One of the linker group amines serves as the nucleophile to open the oxirane moiety and create a compound in which one of the amines of the linker is covalently attached to a carbon which is adjacent to the carbon with the resulting hydroxy group. The resulting compound is referred to in Webb et al. as a polymer support/linker. This compound is subsequently coupled to a nucleoside by reacting nucleoside-pentachlorophenyl succinate with the polymer support/linker, whereby the free amine of the linker displaces the pentachlorophenyl on the succinate (col. 4, lines 7-15). Thus, the first nucleoside monomer is conjugated to the support via 2 linkers: $H_2N-(CH_2)_a-X-(CH_2)_b-Y-(CH_2)_c-NH_2$ and succinate.

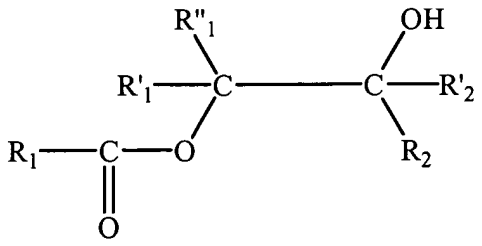
In contrast, the subject amended claims are directed to a method of polynucleotide synthesis in which the polymer is one of R_1, R'_1, R''_1, R_2, and R'_2 in one of the following structures:



(I),



(I'),



(II),

The first nucleotide monomer binds via its 3' or 5' phosphate group to, in the case of structures (I) or (II), the OH on the carbon adjacent to the carbon bearing the Nu or carboxy group. In the case of structure (I'), the epoxide ring is first opened to generate a hydroxy to which the first monomer becomes attached.

One advantage of the subject method relative to Webb et al. is that the subject method provides a universal solid support to which the first and subsequent monomers are added, wherein the universal solid support has a structure that makes it possible for detachment of the finished oligonucleotide by intramolecular nucleophilic displacement (see page 13, line 14 to page 15, line 2 of the specification). In contrast, Webb et al. provide a support with two linkers and a nucleoside, upon which subsequent steps of oligonucleotide synthesis proceeds. The Webb support is not universal in the sense that the first nucleoside must be attached to the support-first linker with a succinate linker. Further, the resulting polymer-linker-linker-nucleoside of Webb et al. is not designed to undergo intramolecular nucleophilic displacement upon complete oligonucleotide synthesis.

The universal support of the subject method also has the advantage of permitting the use of the same monomer reagent and reaction conditions for the very first base as for all subsequent bases (page 6, lines 23-29, and page 7, line 32 to page 8, line 1 of the specification). In contrast, the first monomer of Webb is a nucleoside attached to a pentachlorophenyl succinate and may be considered to be part of the support (col. 4, lines 7-11).

In view of the foregoing distinctive features of the subject method as compared to those of Webb et al., it is submitted that Webb et al. do not anticipate the subject claims. It is also submitted that Webb et al. do not render the amended claims *prima facie* obvious due to the unexpected advantage of a universal support which permits use of the same monomer reagent and reaction conditions for the first monomer as for all

subsequent monomers, and at the same time, the advantage of a single step (using intramolecular nucleophilic displacement) to generate a final oligonucleotide with a free 3' or 5' OH group. Design of such a universal support has hitherto been considered as inconceivable due to what was considered to be two conflicting goals (page 6, lines 23-29 of the specification). The subject claims are therefore submitted to be novel and non-obvious over Webb et al., and withdrawal of the prior art rejection is respectfully requested.

The Phone Interview of August 20, 2003

The undersigned thanks the Examiner for the courtesy and advice extended during the phone interview of August 20, 2003. The Examiner raised several points in relation to a draft response and claim set submitted on August 6, 2003, for his consideration.

The Examiner inquired whether structure (II) of claim 110 had R_1 in the correct location, i.e., whether Applicants instead intended that R_1 be located on the C adjacent to the OH bearing C. Applicants in fact do intend to claim the method with structure (II) in its present form. The Examiner is directed to page 14, lines 7-12, for a discussion regarding this structure.

The Examiner indicated that because the epoxide structure (I') required an additional step of ring opening that was not required for (I) or (II), the proposed method claim would have to clearly accommodate that extra step for (I') only. It is believed that the above claim 110 does clearly provide for the extra process step for structure (I'). Also, claim 113 accommodates the extra ring opening step for structure (II'b) to convert it to structure (I).

The Examiner also indicated that any process steps relating to addition of first and additional nucleotide monomers would need to indicate monomer structure and reagents, and that the final step relating to cleaving of the oligonucleotide from the support would have to specify how the desired free 3' or 5'OH group on the oligonucleotide is generated. It is believed that the above claim 110 addresses these concerns. Specifically, Applicants have added reagents for the monomer extension cycles, and have specified a mechanism in step (f) which indicates how the desired free 3' or 5'OH group is obtained. Applicants wish to point out that steps in claim 110 relating the synthetic addition/extension cycles

involving various nucleotide monomers, are known, conventional prior art methods. Steps in claim 110 relating to the structure of the universal solid support and the final cleaving process to produce the finished oligonucleotide with free 3' or 5' OH, are steps that distinguish over the prior art methods including Webb et al.

The Examiner is invited to phone the undersigned with any additional comments if it is believed that it would expedite prosecution.

Closing Remarks

It is believed that the foregoing amendments and arguments bring the subject application into condition for allowance and notification of same is respectfully requested.

Submitted herewith is a Petition for Extension of Time and a check for $128.00 for the one month extension and the new claims fee. It is believed that no other fees are due with this submission. If this is in error, please charge any necessary fees to Deposit Account No. 19-5117.

Respectfully submitted,

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Enclosures
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